REMARKS

Claims 1-50 are pending. Claims 1-7, 9-11, 13-29, 31-34, and 44-50 are rejected. Claims 2, 4, 15, 22, 35-43, 46, and 50 are canceled without prejudice. Claims 8, 12, and 30 are withdrawn, but Applicants question the withdrawal of claim 8 as not elected, because Applicants elected "lung" as location of transmigration, which is recited in claim 8. Thus, Applicants respectfully requests that claim 8 be reinstated. Claims 1, 10, 14, 16, 20, 21, 27, 44, 48, and 49 are amended to remove non-elected embodiments. Claim 49 is also amended to incorporate the preamble language into the body of the claim. The amendments are therefore fully supported in the application as filed, and incorporate no new matter.

CLAIM OBJECTIONS

Claims 1-4, 9, 10, 15, 16, 20, 22, 29, 32, 33, 46, 48, and 50 are objected to because they encompass nonelected species. Applicants have amended these claims to remove nonelected species, rendering this objection moot, and Applicants request its withdrawal.

CLAIM REJECTIONS UNDER 37 USC §112

Claims 1-7, 14-23, 27, 28, and 44-50 are rejected under 37 USC §112 ¶1 as not enabled and not described.

Applicants believe that the Examiner has acknowledged that amended claims 1-7, 14-23, 27, 28, and 44-50 are enabled. For example, the Examiner's acknowledgement "...the specification, while being enabling for a method of inhibiting at least one of eosinophil recruitment or eosinophil function by administering monokine induced by interferon γ (MIG) or IP-10..." and "Furthermore, while the specification is enabling for inhibiting an eosinophil response to eotaxin-1, eotaxin-2 and IL-13..." (page 3, January 31, 2006 Office Action).

The following description rejection therefore applies only to claim 4, now canceled without prejudice:

> There are two species of the claimed genera disclosed that is within the scope of the claimed genus, *i.e. MIG and IP-10*. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described. There is substantial variability among the species. The specification only described MIG in great detail and IP-10 to a lesser extent. There is no disclosure of proteins homologous to or peptides derived from MIG or IP-10 in the specification (Office Action page 8, emphasis in original)

Thus Applicants believe this rejection is overcome with respect to claim 4, and was improperly applied to claims 1-3, 5-7, 14-23, 27, 28, and 44-50.

Claims 1, 4, 6, 7, 27, 44, and 48 are rejected under 37 USC §112 ¶2 as not distinctly claimed.

Claim 4 reciting "protein homologous to MIG or IP-10" is canceled without prejudice, rendering this rejection moot.

Claim 27 recites "negatively regulating an inflammatory cell". One skilled in the art appreciates that a cytokine "negatively regulating" an inflammatory cell down regulates the inflammatory cell's intrinsic ability to provide a pro-inflammatory response. This could be determined, for example, by measuring the reduction in its secretion of pro-inflammatory agents, its cell-cell contact, its activation of other cells in a pro-

inflammatory cascade, etc. Thus, Applicants disagree that the metes and bounds of claim 27 cannot be determined.

Claim 44 recites "negatively affecting at least one of eosinophil chemoattraction or eosinophil activation activity". One skilled in the art appreciates that "negatively affecting" is a decrease or inhibition, in quantity and/or quality, of chemoattraction or activation in the presence of the cytokine. Thus, Applicants disagree that the metes and bound of claim 44 cannot be determined, e.g., qualitative and/or quantitative chemoattraction or activation assays in the presence, versus absence, of the cytokine can be determined.

Claims 47 and 48 recite "cytokine such as eotaxin-1 is negatively affected". One skilled in the art appreciates that "negatively affected" is a decrease or inhibition in quantity and/or qualitative function in eotaxin-1 in the presence of the cytokine. Thus, Applicants disagree that the metes and bound of claims 47 and 48 cannot be determined, e.g., qualitative and/or quantitative eotaxin-1assays in the presence, versus absence, of the cytokine can be determined.

Applicants believe they have addressed each of the rejections under 35 U.S.C. §112, ¶¶1 and 2, and thus respectfully request its withdrawal.

CLAIM REJECTIONS UNDER 37 USC §102

Claims 1-5, 9-11, 13-29, 31-33, and 44-50 are rejected under 37 USC §102(b) as anticipated by Kuna. Applicants respectfully disagree.

Applicants' claimed method using MIG and/or IP-10 to inhibit eosinophil recruitment and eosinophil-specific functions is not anticipated by Kuna, at least because Kuna does not disclose or suggest eosinophils at all. Note that the title of D1 is "Method of Inhibiting Pro-Inflammatory Mediator Release from Basophils and Mast Cells". Mast cells are a type of histiocyte involved with histamine release; they are not leukocytes. In fact, Kuna itself teaches that its effect is basophil specific (e.g., page 19, line 35 to page 20, line 13). Kuna also does not disclose MIG.

As known to one skilled in the art, eosinophils are one of the five types of leukocytes (white blood cells). Each of these types has specific properties and functions: (1) polymorphonuclear cells, primarily involved in combating bacterial infections; (2) lymphocytes, primarily involved in immunological reactions; (3) monocytes, primarily involved in combating viral infections; (4) eosinophils, primarily involved in allergies and parasitic diseases; and (5) basophils, primarily involved in cell-mediated immune reactions. Each of these cell types has unique properties and operates by distinct mechanisms.

Kuna's treatment method does not anticipate Applicants' method claiming inhibition of eosinophil functions (receptor internalization being the elected species). At least one reason is that treatment of inflammatory diseases, as Kuna discloses, can occur by mechanisms other than those perturbing eosinophil function and can occur by receptor-independent mechanisms.

The claims recite eosinophil-specific properties, as stated at page 1, line 15 to page 2, line 3 of the specification. For example, the scope of the following pending claims requires specific eosinophil properties:

- Claim 1 is "A method of inhibiting at least one of eosinophil recruitment or eosinophil function comprising ...".
- Independent claim 9 is "A method of reducing allergen-induced eosinophilia..."

- Independent claim 24 is "A method of inhibiting pulmonary eosinophil recruitment..."
- Independent claim 44 is "A method of reducing *in vivo* eosinophil chemoattraction comprising ..."
- While claims 14 and 49 are treatment methods, they require an eosinophil response as a measure of efficacy ("...in an amount sufficient to inhibit an eosinophil response to a chemoattractant" in claim 14; "...thereby inhibiting eosinophil recruitment or eosinophil function" in claim 49).

Regarding recruitment properties, recruitment of eosinophils necessarily differs from recruitment of other cell types. Recruitment of eosinophils would occur, for example, in atopic patents. In contrast, recruitment of polymorphonuclear leukocytes would occur in bacterially-infected patients.

Regarding functional properties, such as Applicants' elected receptor internalization, it is specific to eosinophils because of the specific receptors on eosinophil cell membranes. The methods using MIG and/or IP-10 inhibit eosinophil recruitment or functions. While such a method would not be indicated for a patient with a bacterial infection, the claimed method would certainly be indicated for an atopic patient, or a patient with a parasitic infection, or a patient with eosinophilia.

Kuna does not disclose or suggest these specific indications based upon a specific cellular (i.e., eosinophilic) function. Rather, Kuna broadly discloses "inhibiting pro-inflammatory mediator release from basophils or mast cells to treat an inflammatory disease" using IP-10 and other proteins, among which MIG is not listed.

Disease treatment would not disclose or render obvious the claimed eosinophil functions (transmigration, degranulation, receptor expression, etc.). At least one reason is that treatment of inflammatory diseases, as Kuna discloses, can occur by mechanisms other than those perturbing eosinophil function and can occur by receptor-independent mechanisms.

Thus, Kuna's site of action is limited to basophils and mast cells, which are characterized as "primary allergic cells" (page 5, line 6; page 19, beginning at line 35). In contrast, Applicants' claims recite eosinophils. Kuna discloses inhibition of pro-inflammatory mediator release, i.e., outcomes derived from biochemical action. In contrast, Applicants' claims modulate cellular function, among which is the elected species of receptor internalization in addition to biochemical affects. Physiological triggers or outcomes of eosinophilia are not exclusive to the triggers or outcomes of allergic reactions or inflammatory diseases.

For at least these reasons, Applicants believe the rejection under 35 §102(b) is overcome and respectfully request its withdrawal.

CLAIM REJECTIONS UNDER 37 USC §103

Claims 1-5, 14-29, 31-33, and 44-50 are rejected under 37 USC §103(a) as obvious over Kuna in view of Loetscher and Kaplan.

Applicants dispute that Kuna is properly combined with Loetscher. Kuna has been distinguished above, and Applicants incorporate their analysis distinguishing Kuna. Applicants' claims are entirely eosinophil specific, and do not recite any cell type other than eosinophils. All of Applicants claims recite MIG and/or IP-10. At least because Kuna does not disclose eosinophils, nor does Kuna disclose MIG, Applicants respectfully assert that one skilled in the art would not be taught, motivated, or suggested to look to the combination of Kuna with Loetscher in Applicants' methods.

Even if Kuna were properly combined with Loetscher, it would not result in Applicants' method because Loetscher teaches an alternate result based on a different mechanism.

The Examiner states Loetscher teaches

> ...that MIG and IP-10 are expressed on Th1 cells while CCR3, the receptor for eotaxin and several other CC chemokines is characteristic of Th2 cells. MIG and IP-10 complete for binding of eotaxin to CCR3-bearing cells and inhibit migration and Ca2+ changes induced in such cells by eotaxin and eotaxin-2 (Office Action, 2nd ¶, page 12),

i.e., MIG and IP-10 are competitive antagonists of eotaxin binding to the CCR3 receptor.

However, Applicants' claims do not recite this action and Applicants teach that MIG and IP-10's inhibition of eosinophil migration is not a result of competitive antagonism at the CCR3 receptor.

> To determine if CCR3 was the MIG receptor in eosinophils, the ability of MIG to compete for the binding of biotinylated eotaxin-1 to eosinophils was determined. While unlabeled eotaxin-1 or eotaxin-2 was able to compete for biotinylated eotaxin-1 binding to eosinophils, unlabeled MIG at doses up to 10 μM did not inhibit the binding [of] CCR3 ligands (page 31, line 22 to page 32, line 2).

Kaplan is a review article that does not cure the deficiencies of Kuna (different cells) and Loetscher (different mechanism), such that one skilled in the art would have no reasonable expectation of success to achieve Applicants' method.

At least for these reasons, Applicants respectfully assert that Kuna in view of Loetscher and Kaplan does not render obvious claims 1-5, 14-29, 31-33, and 44-50.

Claims 6-7 are rejected under 37 USC §103(a) as obvious over Kuna in view of Loetscher and further in view of Bates.

Applicants incorporate the above analysis distinguishing Kuna and Loetscher. Bates discloses that eosinophil priming by IL-5 prior to chemotactic agent administration is required to elicit an increase in ERK1/ERK2 phosphorylation by the chemotactic agent. Bates discloses this priming effect as specific to the IL-5 family of cytokines, and does not teach, suggest, or motivate the ability of any other factor, such as MIG, to affect ERK1/ERK2 phosphorylation.

Further, Applicants have shown that MIG alone has no effect on ERK1/ERK2 phosphorylation, but in combination with eotaxin-2, ERK1/ERK2 is phosphorylated to a greater extent than with just eotaxin-2 alone (page 33, lines 1-5). Thus, Bates teaches away from Applicants' method because Bates suggests that a decrease in ERK1/ERK2 phosphorylation may prevent eosinophilia.

Claim 34 is rejected under 37 USC §103(a) as obvious over Kuna in view of Loetscher and Schmid-Grendelmeier.

Applicants incorporate the above analysis distinguishing Kuna and Loetscher. Schmid-Grendelmeier does not cure these deficiencies.

Schmid-Grendelmeier teaches that eotaxin stimulates IL-13 release from eosinophils. However, as previously analyzed, MIG is not a simple competitive antagonist of eotaxin. Applicants' method recites MIG administered to an asthmatic patient inhibiting an IL-13 associated asthmatic response. None of Kuna, Loetscher, nor Schmid-Grendelmeier teach, suggest, or motivate the effects of MIG on an IL-13 response.

Claims 1 and 2 are rejected under 35 USC §103(a) as obvious over Loetscher. Claim 2 is canceled, rendering its rejection moot.

To establish a prima facie case, Loetscher must, when considered as a whole, teach or suggest Applicants' claimed method to inhibit eosinophil recruitment or function by administering MIG and/or IP-10 in a amount to inhibit eosinophil receptor internalization, or demonstrate that one skilled in the art would know to modify Loetscher to result in Applicants' method. MPEP § 2142. Parts of Loetscher cannot be selectively used to support a given position while excluding other parts necessary to appreciate what Loetscher as a whole suggests. MPEP §2141 II (B).

As previously analyzed, the Examiner states that Loetscher teaches that "MIG and IP-10 compete for binding of eotaxin to CCR3-bearing cells" (Office Action, 2nd ¶, page 12). One skilled in the art, based on Loetscher, would be taught that MIG and IP-10 competing with endogenous eotaxin would result in increased chances that a ligand (eotaxin, MIG, or IP-10) would bind to the CCR3 receptor. Because one skilled in the art appreciates receptor binding initiates receptor internalization, he/she would therefore expect increase in receptor internalization when MIG and/or IP-10 is administered. However, Applicants' claim 1 recites a method where MIG and/or IP-10 is administered to inhibit eosinophil internalization. Thus, Loetscher does not teach or suggest all embodiment of Applicant's claim 1. In fact, Loetscher teaches away from Applicant's claim 1, as analyzed.

For at least this reason, Applicants assert that Loetscher does not render claim 1 obvious, and request the rejection be withdrawn.

CONCLUSION

Applicants believe this application is now in complete condition for allowance, and that no fee is due. If fees or surcharges are deemed due, Applicants authorize charging them to Deposit Account No. 23-3000.

The Examiner is invited to contact Applicants' undersigned representative with any questions or issues.

Respectfully submitted,
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